Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants would like to note that responsibility for prosecution of the present application has been transferred to Nixon Peabody LLP (Customer No. 26774). Revocation and power of attorney forms are being processed for subsequent submission in this application. The undersigned attorney has authority to act on behalf of the applicants in this application.

Claims 1, 14, and 15 have been amended, and presently withdrawn claims 7, 8, and 34-49 have been cancelled without prejudice. Claim 1 has been amended to recite that the polymer matrix is an affinity resin. Descriptive support for this limitation appears at page 7, line 24.

New claims 53 and 54 have been introduced. Descriptive support for the subject matter of claim 53 appears at page 7, lines 22-25. Descriptive support for the subject matter of claim 54 appears in the recitation of the preferred affinity resin, e.g., Toyopearl™ amino 650 M, as discussed below. No new matter has been introduced.

Claim 1 is directed to a method limited to the use of an affinity resin that has never before been proven to bind to prion protein in a specific and selective manner. The inventors believe that it is the *combination* of the affinity matrix with the functional groups that enable the specific and selective binding with prion. This was totally unexpected and could never have been predicted by the prior art. The deficiencies of the prior art are discussed specifically below.

The rejection of claims 14 and 15 under 35 U.S.C. § 112 (second paragraph) for indefiniteness is respectfully traversed in view of the accompanying amendments and the following remarks.

The rejected claims have been amended to replace the tradename with the structural or functional description of the resins available from their manufacture. Applicants submit that the person of ordinary skill in the art would have fully appreciated—at the time the present application was filed—that the tradename and the product descriptions are synonymous. As identified at page 12 of the present application, FRACTOGEL®, TOYOPEARL™, and TSK-GEL™ were products available from Tosoh Bioscience

(Montgomery, PA). That the structural properties of these resins would have been known to the person of skill in the art is evidenced by the attached **Exhibits 1-3**.

Exhibit 1 is a product specification sheet for FRACTOGEL® EMD, which makes clear that the product is a porous, beaded methacrylate resin material derivatized with hydrophilic linear polymer chains. In particular, **Exhibit 1** recites as follows:

> *The Matrix*
> The structure of the Fractogel® particles is considerably different from that of other hydrophilic chromatographic resins like dextran, agarose or cellulose. Fractogel® is a synthetic methacrylate based polymeric resin providing excellent pressure stability resulting in high flow rates. The process media consist of beads with a particle size between 40 and 90 µm. Fractogel® EMD BioSEC for size exclusion chromatography and the high-resolution S-type ion exchangers have a particle size in the range of 20-40 µm. The pores which are formed from intertwined polymer agglomerates, have a size of about 800Å enabling a free diffusion of proteins into the beads. The complete surface is strongly hydrophilic due to the ether linkages in the polymer.
>
> *The Tentacles*
> Long, linear polymer chains ("tentacles") carry the functional ligands. All tentacles are covalently attached to hydroxyl groups of the backbone structure of Fractogel®. Thus, both the bead and surface modification are stable to regeneration and sanitization. The main advantage of the tentacle chemistry is the large amount of sterically accessible ligands for the binding of biomolecules without any steric hindrance. Therefore target biomolecules are much more tightly bound during the separation process. Different ligands are utilised for various application areas (ion exchange, affinity-, hydrophobic interaction chromatography).

Exhibit 1 at page 3.

Exhibit 2 is a product specification sheet for Toyopearl™ and TSK-GEL™ size exclusion resins. It is clear that both of these resins are similar in structure, but vary in their degree of cross-linking. Both of these resins are characterized as porous beaded methacrylate resin material derivatized with hydroxylic functionalities, and have the structure:

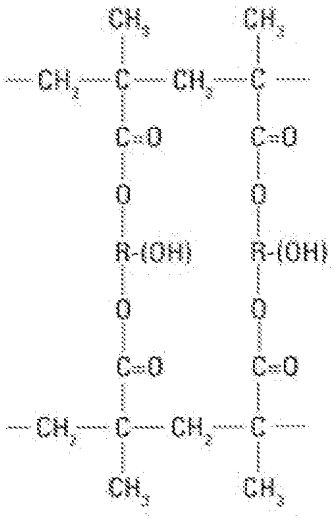


Exhibit 2 at page 1. Also noted on page 3 of **Exhibit 2** is the fact that Toyopearl™ HW 65 is characterized by a mean particle size of ~65 μm and a mean pore size of 1000Å.

Exhibit 3 is a product specification sheet for Toyopearl™ Amino 650, which is a resin defined as a porous beaded methacrylate resin material derivatized with hydrophilic spacer chains that terminate in a primary amino group. This resin is characterized by the following chemical structure:

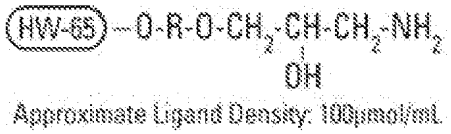


Exhibit 3 at page 1. Also noted on page 1, the M-grade indicates a mean particle size of 65 μm.

Because the person of skill in the art would fully appreciate that the tradenames listed in original claims 14 and 15 are synonymous with the types of resins presently recited, the rejection of claims 14 and 15 for indefiniteness is improper and should be withdrawn.

The rejection of claims 1, 2, 5, 6, 9-33, and 50-52 under 35 U.S.C. § 102(b) as anticipated by Foster et al., *Vox Sanguinis* 78:86-95 (2000) ("Foster") as evidenced by the Affinity Chromatography data sheet, Cat #28 A21DS ("Affinity data sheet") is respectfully traversed.

Foster discloses a method for manufacturing plasma proteins using various steps of precipitation as well as a DEAE Toyopearl™ 650 M ion exchange resin during factor VIII preparation.

Claim 1 presently recites a method of detecting and separating a prion protein from a sample that includes the following limitations: (i) the feature that "the binding material is capable of binding specifically and selectively to the prion protein"; and (ii) the feature that "the polymer matrix is an affinity resin."

For the reasons discussed below, Foster fails to teach both of these features and the Affinity data sheet does not overcome these deficiencies.

Firstly, Foster fails to teach or suggest the use of a resin that is capable of binding specifically and selectively to the prion protein as claimed.

In the present application, the applicants compared both strong and weak ion exchange resins, and found that none of them worked as well as affinity resin, such as the Toyopearl™ Amino 650M. The data is summarized in Table 1 of the present application. In particular, line 11 of Table 1 shows the binding results for DEAE Toyopearl™ 650M as being weakly positive (+), which is far inferior to the strongly positive results obtained using Toyopearl™ Amino 650 M (+++). The applicants have clearly demonstrated therefore that there are significant differences in the binding ability of prion protein by the prior art resin, DEAE Toyopearl™ 650 M, and a favored resin of the present invention, Toyopearl™ Amino 650 M, which is capable of specific and selective binding to prion protein.

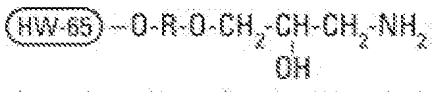
The applicants of the present invention have therefore demonstrated that DEAE Toyopearl™ 650 M disclosed in Foster is incapable of removing prion protein by any specific and selective binding between the prion binding material (i.e., the resin) and prion protein. This proves that Foster does not disclose a prion protein binding material that is capable of binding specifically and selectively to the prion protein as required by Claim 1. Therefore, because Claim 1 is limited to a method which uses a binding material that binds specifically and selectively to the prion protein, it must be novel over Foster.

Secondly, at page 3 of the Office Action, the PTO asserts (incorrectly) that Foster uses Toyopearl™ amino 650M, and at page 4 of the Office Action the PTO asserts that the "prion binding material disclosed by Foster et al is exactly the same as the prion binding material used in the currently claimed method." Both of these statements are incorrect.

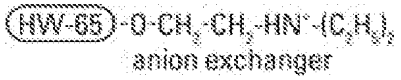
Foster uses DEAE Toyopearl™ 650 M ion exchange resin, which is not the same as Toyopearl™ Amino 650 M. These two resins are structurally, chemically and functionally very different ligands. DEAE Toyopearl™ 650 M ion exchange resin stands for

di-ethylamino ethyl (DEAE) modified Toyopearl™ 650 M, and is a weak ion exchanger. In contrast, Toyopearl™ amino 650 M is the base resin that Tosoh BioSciences recommends as *an affinity resin*; it is not an ion exchange resin.

The Toyopearl™ amino 650 M is structurally distinct of the DEAE Toyopearl™ 650 M used by Foster. Indeed, as shown above and reproduced below, Toyopearl™ amino 650 M has the following structure:



whereas DEAE Toyopearl™ 650 has the following structure:



See *Ion Exchange Chromotography, In* Tosoh Bioscience Catalog, pp. 13-20 (attached hereto as **Exhibit 4**) at 15, Table II. Thus, the two products are not the same, and as explained above, the results achieved with these two resins are very different.

Thirdly, Foster fails to teach or suggest the use of a polymer matrix that is an affinity resin. Ion exchange resins such as DEAE Toyopearl 650 M work by exchanging ions between the prion protein and the ion exchanger (the resin), i.e., interaction between positive and negative charges. Ion exchangers are either cation exchangers for positively charged cations or anion exchangers for negatively charged anions. DEAE Toyopearl 650 M is an anion exchanger.

However, in contrast, affinity resins work by a highly specific biochemical interaction between the resin and the prion proteins. No exchange of ions occurs in affinity resins. In contrast, binding is dependent on the respective structures of the binding material and the prion. The mechanism of affinity chromatography is physically different from ion exchange.

In view of the foregoing, it is clear that Foster does not teach or suggest use of an affinity resin, and that the Foster ion exchange resin, DEAE Toyopearl 650 M, does not bind specifically and selectively to the prion protein as required by claim 1. Because claim 1 is limited to a method which uses a polymer matrix that is an *affinity* resin that binds *specifically and selectively* to the prion protein, the claimed method must be novel over Foster.

In addition to the foregoing, applicants further submit that the claimed subject matter would not have been obvious over Foster, either alone or in combination with the Affinity data sheet. Foster merely assumes that the prion protein remained bound to the ion exchange resin. Indeed, Foster recites as follows:

> It is possible that PrPsc may have *partitioned* into wash fractions which were not sampled; however, it seems more probable, given its adherent nature [16], that most PrPsc remained adsorbed to chromatographic matrices following product elution.

Foster at 92 (emphasis added). Upon reading the above-quoted statement in Foster, one of skill in the art would conclude that PrPsc, because of its "adherent nature", would bind to almost anything. Applicants therefore submit that the "partitioning" statement of Foster argues against specificity and selectively, i.e., away from the claimed invention. In Foster, use of the ion exchange resin DEAE Toyopearl 650M results in non-selective and non-specific binding for prion protein, i.e., partitioning or size exclusion of large aggregates. Hence, proteins (such as blood proteins) other than prions also bind to the resin due to non-specific and non-selective interactions between these proteins and the ion exchange resin. A problem with this resin, therefore, is that proteins in the blood other than prions are also bound non-specifically and non-selectively to the column. This makes detecting, separation, and subsequent analysis of the prion proteins in the sample very difficult when using this inferior prior art resin.

In contrast to the results of Foster, the present application clearly demonstrates the binding of only prion protein to the resin in a selective and specific manner. Subsequent elution therefrom and accurate analysis of the pure prion protein is then possible. Furthermore, advantageously, no other blood proteins are bound to the resin. This high specificity and selectively is a significant advantage achieved by the method of claim 1.

For these reasons, the rejection of claims 1, 2, 5, 6, 9-33, and 50-52 as anticipated by Foster is improper and should be withdrawn.

The rejection of claims 1, 2, 5, 6, and 9-33 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,750,025 to Hammond et al. ("Hammond") is respectfully traversed.

Hammond discloses a method of detecting the presence of a prion protein in a sample involving the use of streptavidin for separating prions from other proteins. While the PTO recognized the mention of "Toyopearl" at column 5, lines 6-17, this use of the resin

requires the presence of streptavidin bound to the resin and does not necessarily involve use of a "binding material that is capable of binding specifically and selectively to the prion protein." Indeed, streptavidin does not bind specifically and selectively to the prion protein.

The PTO also refers to the disclosure of Toyopearl Amino 650 M at column 10, lines 44-46. This language of Hammond, however, relates not to the binding of prion proteins but instead to the synthesis of peptides by standard Fmoc chemistry directly onto the resin. A careful reading of the entire paragraph cited by the PTO confirms as much. Hence, Hammond does not disclose the use of the Toyopearl Amino 650 M resin for detecting and separating prion proteins.

Because Hammond fails to disclose a binding material that is capable of binding specifically and selectively to the prion protein, as required by claim 1, and Hammond fails to recite use of an affinity resin as the polymer matrix, Hammond cannot anticipate the presently claimed invention.

Applicants further submit that the presently claimed invention would not have been obvious over Hammond. Hammond does not even consider the problems inherent with using non-specific and non-selective resins, i.e., that they also bind other proteins present in blood and serum. There is also no recognition by Hammond, when using streptavidin bound to a resin, that the resin should be one that is capable of binding specifically and selectively to the prion protein. Hence, Hammond does not teach or suggest each and every limitation of the presently claimed invention.

Therefore, the rejection of claims 1, 2, 5, 6, and 9-33 for anticipation by Hammond is improper and should be withdrawn.

The rejection of claims 1, 2, 5, 6, and 9-33 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,221,614 to Prusiner et al. ("Prusiner") in view of Kragten et al., *J. Biol. Chem.* 273:5821-5828 (1998) ("Kragten") and the Affinity data sheet is respectfully traversed.

Prusiner teaches the use of a polymer coated with a prion complexing agent, which is used in chromatography to physically separate the prion bound to the complexing agent from a solution such as blood or plasma. The complexing agent, such as an antibody or phosphotungstic acid or trichloroacetic acid, a combination thereof, is immobilized on the chromatography bead or resin.

Kragten teaches a putative mechanism of action for the drug R-Deprenyl, which is used for the treatment of Parkison's disease. Kragten specifically reports the

detection of an interaction between R-Deprenyl and the related compound CGP-3466 with glyceraldehyde-3-phosphate dehydrogenase. This was accomplished using affinity chromatography that employed R-Deprenyl or CGP-3466 immobilized on Toyopearl™ AF 650M.

The Affinity data sheet is relied upon merely for the known use of Toyopearl™ AF 650M as a substrate used for protein purification.

Applicants submit that the rejection is improper for several reasons.

Firstly, Kragten is irrelevant to the claimed invention and is not properly combinable with Prusiner (and the Affinity data sheet), because Kragten is not analogous art. The Federal Circuit has set forth a two-pronged test to determine whether a reference constitutes analogous art. *In re Clay,* 966 F.2d 656, 658-59, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992). The test considers:

> (1) Whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.

Id. In this case, the present invention relates to the specific and selective detection and separation of prion protein from a sample. The person skilled in the art in relation to the present invention will be skilled in the performance of protein separations. As noted above, Kragten is concerned with the mechanism of action for the drug R-Deprenyl, which is used for the treatment of Parkinson's disease. The field of Parkinson's disease therapeutics is entirely unrelated to prion protein detection. There is nothing even remotely relevant to the specific and selective separation of prion protein from a sample. While Kragten describes the use of a modified Toyopearl™ AF amino 650M resin during chromatography, Kragten's use of the resin is irrelevant to use of this resin for specific and selective binding to prion proteins. Therefore, persons skilled in the art of protein separation and detection would have been unlikely to consider the teachings of Kragten when designing the method as presently claimed. For the foregoing reasons, Kragten is not properly combinable with Prusiner (and the Affinity data sheet).

Secondly, even if—assuming *arguendo*—Kragten is properly combinable (which applicants do not admit), then there is nothing in the combination of Prusiner with Kragten and the Affinity data sheet that would lead a person of ordinary skill to perform the method as presently claimed. In particular, none of the cited references identify or suggest "a

polymeric prion protein binding material … compris[ing] a matrix bound to a functional group, … wherein the binding material is capable of binding specifically and selectively to the prion protein."

Prusiner, as noted above, requires the presence of a complexing agent to bind prion protein. Thus, Prusiner does not teach *a polymeric prion protein binding material* as recited, and based on Kragten and the Affinity data sheet, there would not have been any motivation to use the Toyopearl AF amino 650 M of Kragten in the presently claimed invention. While Kragten certainly discloses the use of the preferred resin, it is for an altogether different purpose that is not even remotely relevant to separation and detection of prion protein. Accordingly, the person of skill in the art would not have had any motivation to combine the teachings of Prusiner with the teachings of Kragten, and would therefore never have resulted in the method recited in amended claim 1.

For these reasons, the rejection of claims 1, 2, 5, 6, and 9-33 for obviousness over Prusiner in view of Kragten and the Affinity data sheet is improper and should be withdrawn.

The provisional rejection of claims 1, 2, 5, 6, and 8-33 under the judicially created doctrine of obviousness-type doubling patenting over claims 1-20 of copending U.S. Patent Application Serial No. 10/962,670 to Hammond et al. ("Hammond II") is respectfully traversed in view of the amendments above and as submitted in the co-pending application.

Under circumstances where the only outstanding rejection is a provisional double-patenting rejections (and applicants submit all other rejections should be withdrawn for the reasons noted above), it is within applicants' right to demand withdrawal of the provisional rejection. Because the present application is earlier-filed relative to Hammond II, applicants respectfully request withdrawal of the provisional rejection.

Applicants also submit that new claims 53 and 54 are patentable over the art of record. As mentioned above, Foster discloses the use of DEAE Toyopearl 650 M *ion exchange resin*, and claims 53 and 54 are therefore novel over this citation. Hammond does not disclose use of an affinity matrix. Claims 53 is inventive because, as discussed in detail above, it was not obvious that the use of an affinity matrix would be able to specifically and selectively bind to prion protein. Claim 54 is novel over Hammond, which uses a matrix that is not covalently attached to the functional group (i.e. ligand). Claim 54 is inventive over the prior art of record, because none of the cited art teaches or suggests use of a polymer matrix

having a polymeric backbone covalently attached to the functional group. For these reasons, both of claims 53 and 54 should be allowable.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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